

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
17 July 2003 (17.07.2003)

PCT

(10) International Publication Number
WO 03/057170 A2

(51) International Patent Classification⁷: **A61K**

(21) International Application Number: **PCT/US03/00337**

(22) International Filing Date: 7 January 2003 (07.01.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/346,746	7 January 2002 (07.01.2002)	US
60/347,312	9 January 2002 (09.01.2002)	US
60/368,617	29 March 2002 (29.03.2002)	US
60/374,979	23 April 2002 (23.04.2002)	US
60/389,364	17 June 2002 (17.06.2002)	US
10/237,138	6 September 2002 (06.09.2002)	US

(71) Applicant (for all designated States except US): **EMI-SPHERE TECHNOLOGIES, INC.** [US/US]; 765 Old Saw Mill River Road, Tarrytown, NY 10591 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **JARBIT, Ehud**

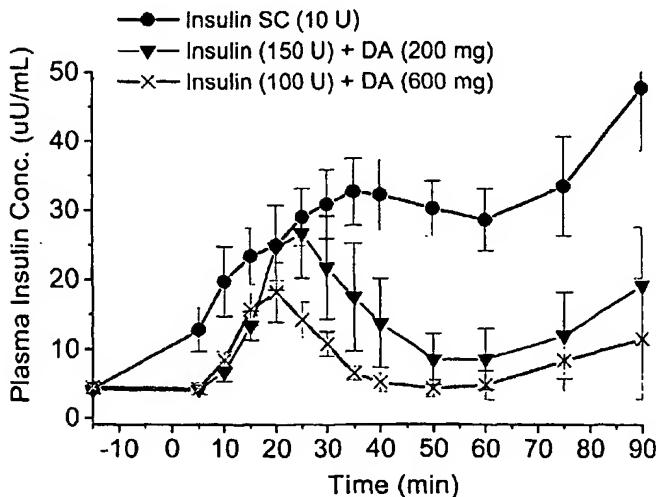
[US/US]; 765 Old Saw Mill River Road, Tarrytown, NY 10591 (US). **ABbas, Richat** [US/US]; 3705 Marcy Street, Mohegan Lake, NY 10547 (US). **GOLDBERG, Michael** [US/US]; 765 Old Saw Mill River Road, Tarrytown, NY 10591 (US). **WOOD, T., Cooper** [US/US]; 2nd Floor, 24 First Avenue, New York, NY 10009 (US). **DINH, Steven** [US/US]; 765 Old Saw Mill River Road, Tarrytown, NY 10591 (US). **WONG, Vivien** [US/US]; 765 Old Saw Mill River Road, Tarrytown, NY 10591 (US).

(74) Agents: **DAVIDSON, Clifford, M. et al.**; Davidson, Davidson & Kappel, LLC, 14th Floor, 485 Seventh Avenue, New York, NY 10018 (US).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

[Continued on next page]

(54) Title: ORAL INSULIN THERAPY



WO 03/057170 A2

(57) Abstract: Pharmaceutical dosage forms for oral administration to a patient for the treatment of diabetes, comprising insulin and a delivery agent that facilitates insulin transport in a therapeutically effective amount to the bloodstream and that result in a lower incidence of vascular diseases associated with the repeated administration of insulin are disclosed. Also disclosed is a method of attenuating the undesirable incidence of diseases associated with chronic dosing of insulin is provided whereby the oral administration to a patient of insulin along with a suitable delivery agent that facilitates the absorption of insulin from the gastrointestinal tract of the patient in a therapeutically effective amount, for treatment of diabetes.



(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference
(if desired) (12 characters maximum) 817.1009PCT

Box No. I TITLE OF INVENTION
ORAL INSULIN THERAPY

Box No. II APPLICANT

This person is also inventor

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

Emisphere Technologies, Inc.
765 Old Saw Mill River Road
Tarrytown, NY 10591

Telephone No.
(914) 347-2220

Facsimile No.
(914) 347-2498

Teleprinter No.

Applicant's registration No. with the Office

State (that is, country) of nationality:
US

State (that is, country) of residence:
US

This person is applicant for the purposes of: all designated States all designated States except the United States of America the United States of America only the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

Ehud Arbit
765 Old Saw Mill River Road
Tarrytown, NY 10591

This person is:

- applicant only
- applicant and inventor
- inventor only (If this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:
US

State (that is, country) of residence:
US

This person is applicant for the purposes of: all designated States all designated States except the United States of America the United States of America only the States indicated in the Supplemental Box

Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:

agent common representative

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

Davidson, Davidson & Kappel, LLC
485 Seventh Avenue, 14th Floor
New York, NY 10018, UNITED STATES of AMERICA
Davidson, Clifford M. ; Davidson, Leslye B. ; Kappel, Cary S. ; Gehris, William C. ; Wildes, Morey B. ; Paradiso, Robert J. ; Swanson, Erik R. ; Carty, Thomas P.; and all other attorneys and agents at Davidson, Davidson & Kappel, LLC

Telephone No.
(212) 736-1940

Facsimile No.
(212) 736-2427

Teleprinter No.

Agent's registration No. with the Office

Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

Richat Abbas
3705 Marcy Street
Mohegan Lake, NY 10547

This person is:

- applicant only
- applicant and inventor
- inventor only (If this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:
USState (that is, country) of residence:
US

This person is applicant for the purposes of: all designated States all designated States except the United States of America the United States of America only the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

Michael Goldberg
765 Old Saw Mill River Road
Tarrytown, NY 10591

This person is:

- applicant only
- applicant and inventor
- inventor only (If this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:
USState (that is, country) of residence:
US

This person is applicant for the purposes of: all designated States all designated States except the United States of America the United States of America only the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

T. Cooper Woods
24 First Avenue, 2nd Floor
New York, N.Y. 10009

This person is:

- applicant only
- applicant and inventor
- inventor only (If this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:
USState (that is, country) of residence:
US

This person is applicant for the purposes of: all designated States all designated States except the United States of America the United States of America only the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

Steven Dinh
765 Old Saw Mill River Road
Tarrytown, NY 10591

This person is:

- applicant only
- applicant and inventor
- inventor only (If this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:
USState (that is, country) of residence:
US

This person is applicant for the purposes of: all designated States all designated States except the United States of America the United States of America only the States indicated in the Supplemental Box

Further applicants and/or (further) inventors are indicated on another continuation sheet.

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

Vivien Wong
765 Old Saw Mill River Road
Tarrytown, NY 10591

This person is:

- applicant only
 applicant and inventor
 inventor only (If this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:
USState (that is, country) of residence:
US

This person is applicant for the purposes of: all designated States all designated States except the United States of America the United States of America only the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

- applicant only
 applicant and inventor
 inventor only (If this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant for the purposes of: all designated States all designated States except the United States of America the United States of America only the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

- applicant only
 applicant and inventor
 inventor only (If this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant for the purposes of: all designated States all designated States except the United States of America the United States of America only the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

- applicant only
 applicant and inventor
 inventor only (If this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant for the purposes of: all designated States all designated States except the United States of America the United States of America only the States indicated in the Supplemental Box

Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No. V DESIGNATION OF STATES Mark the applicable check-boxes below; at least one must be marked.

The following designations are hereby made under Rule 4.9(a):

Regional Patent

- AP ARIPO Patent: GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, MZ Mozambique, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZM Zambia, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT (*if other kind of protection or treatment desired, specify on dotted line*)
- EA Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- EP European Patent: AT Austria, BE Belgium, CH & LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, TR Turkey, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- OA OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GQ Equatorial Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (*if other kind of protection or treatment desired, specify on dotted line*)

National Patent (*if other kind of protection or treatment desired, specify on dotted line*):

- | | | |
|---|--|--|
| <input checked="" type="checkbox"/> AE United Arab Emirates | <input checked="" type="checkbox"/> GM Gambia | <input checked="" type="checkbox"/> NZ New Zealand |
| <input checked="" type="checkbox"/> AG Antigua and Barbuda | <input checked="" type="checkbox"/> HR Croatia | <input checked="" type="checkbox"/> OM Oman |
| <input checked="" type="checkbox"/> AL Albania | <input checked="" type="checkbox"/> HU Hungary | <input checked="" type="checkbox"/> PH Philippines |
| <input checked="" type="checkbox"/> AM Armenia | <input checked="" type="checkbox"/> ID Indonesia | <input checked="" type="checkbox"/> PL Poland |
| <input checked="" type="checkbox"/> AT Austria | <input checked="" type="checkbox"/> IL Israel | <input checked="" type="checkbox"/> PT Portugal |
| <input checked="" type="checkbox"/> AU Australia | <input checked="" type="checkbox"/> IN India | <input checked="" type="checkbox"/> RO Romania |
| <input checked="" type="checkbox"/> AZ Azerbaijan | <input checked="" type="checkbox"/> IS Iceland | <input checked="" type="checkbox"/> RU Russian Federation |
| <input checked="" type="checkbox"/> BA Bosnia and Herzegovina | <input checked="" type="checkbox"/> JP Japan | <input checked="" type="checkbox"/> SD Sudan |
| <input checked="" type="checkbox"/> BB Barbados | <input checked="" type="checkbox"/> KE Kenya | <input checked="" type="checkbox"/> SE Sweden |
| <input checked="" type="checkbox"/> BG Bulgaria | <input checked="" type="checkbox"/> KG Kyrgyzstan | <input checked="" type="checkbox"/> SG Singapore |
| <input checked="" type="checkbox"/> BR Brazil | <input checked="" type="checkbox"/> KP Democratic People's Republic of Korea | <input checked="" type="checkbox"/> SI Slovenia |
| <input checked="" type="checkbox"/> BY Belarus | <input checked="" type="checkbox"/> KR Republic of Korea | <input checked="" type="checkbox"/> SK Slovakia |
| <input checked="" type="checkbox"/> BZ Belize | <input checked="" type="checkbox"/> KZ Kazakhstan | <input checked="" type="checkbox"/> SL Sierra Leone |
| <input checked="" type="checkbox"/> CA Canada | <input checked="" type="checkbox"/> LC Saint Lucia | <input checked="" type="checkbox"/> TJ Tajikistan |
| <input checked="" type="checkbox"/> CH & LI Switzerland and Liechtenstein | <input checked="" type="checkbox"/> LK Sri Lanka | <input checked="" type="checkbox"/> TM Turkmenistan |
| <input checked="" type="checkbox"/> CN China | <input checked="" type="checkbox"/> LR Liberia | <input checked="" type="checkbox"/> TN Tunisia |
| <input checked="" type="checkbox"/> CO Colombia | <input checked="" type="checkbox"/> LS Lesotho | <input checked="" type="checkbox"/> TR Turkey |
| <input checked="" type="checkbox"/> CR Costa Rica | <input checked="" type="checkbox"/> LT Lithuania | <input checked="" type="checkbox"/> TT Trinidad and Tobago |
| <input checked="" type="checkbox"/> CU Cuba | <input checked="" type="checkbox"/> LU Luxembourg | <input checked="" type="checkbox"/> TZ United Republic of Tanzania |
| <input checked="" type="checkbox"/> CZ Czech Republic | <input checked="" type="checkbox"/> LV Latvia | <input checked="" type="checkbox"/> UA Ukraine |
| <input checked="" type="checkbox"/> DE Germany | <input checked="" type="checkbox"/> MA Morocco | <input checked="" type="checkbox"/> UG Uganda |
| <input checked="" type="checkbox"/> DK Denmark | <input checked="" type="checkbox"/> MD Republic of Moldova | <input checked="" type="checkbox"/> US United States of America |
| <input checked="" type="checkbox"/> DM Dominica | <input checked="" type="checkbox"/> MG Madagascar | <input checked="" type="checkbox"/> UZ Uzbekistan |
| <input checked="" type="checkbox"/> DZ Algeria | <input checked="" type="checkbox"/> MK The former Yugoslav Republic of Macedonia | <input checked="" type="checkbox"/> VN Viet Nam |
| <input checked="" type="checkbox"/> EC Ecuador | <input checked="" type="checkbox"/> MN Mongolia | <input checked="" type="checkbox"/> YU Yugoslavia |
| <input checked="" type="checkbox"/> EE Estonia | <input checked="" type="checkbox"/> MW Malawi | <input checked="" type="checkbox"/> ZA South Africa |
| <input checked="" type="checkbox"/> ES Spain | <input checked="" type="checkbox"/> MX Mexico | <input checked="" type="checkbox"/> ZM Zambia |
| <input checked="" type="checkbox"/> FI Finland | <input checked="" type="checkbox"/> MZ Mozambique | <input checked="" type="checkbox"/> ZW Zimbabwe |
| <input checked="" type="checkbox"/> GB United Kingdom | <input checked="" type="checkbox"/> NO Norway | |
| <input checked="" type="checkbox"/> GD Grenada | | |
| <input checked="" type="checkbox"/> GE Georgia | | |
| <input checked="" type="checkbox"/> GH Ghana | | |

Check-boxes below reserved for designating States which have become party to the PCT after issuance of this sheet:

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (*Confirmation (including fees) must reach the receiving Office within the 15-month time limit.*)

Box No. VI PRIORITY CLAIM					
The priority of the following earlier application(s) is hereby claimed:					
Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:			international application: receiving Office
		national application: country	regional application: regional Office		
item (1) 7 January 2002 (07.01.02)	60/346,746	US			
item (2) 9 January 2002 (09.01.02)	60/347,312	US			
item (3) 29 March 2002 (29.03.02)	60/368,617	US			
item (4) 23 April 2002 (23.04.02)	60/374,979	US			
item (5) 17 June 2002 (17.06.02)	60/389,364	US			

Further priority claims are indicated in the Supplemental Box.

The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (*only if the earlier application was filed with the Office which for the purposes of this international application is the receiving Office*) identified above as:

all items item (1) item (2) item (3) item (4) item (5) other, see Supplemental Box

* Where the earlier application is an ARIPO application, indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed (Rule 4.10(b)(ii)):

Box No. VII INTERNATIONAL SEARCHING AUTHORITY		
Choice of International Searching Authority (ISA) (if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):		
ISA / US		
Request to use results of earlier search; reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority):		
Date (day/month/year)	Number	Country (or regional Office)

Box No. VIII DECLARATIONS		Number of declarations
The following declarations are contained in Boxes Nos. VIII (i) to (v) (mark the applicable check-boxes below and indicate in the right column the number of each type of declaration):		
<input type="checkbox"/>	Box No. VIII (i) Declaration as to the identity of the inventor	
<input type="checkbox"/>	Box No. VIII (ii) Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	
<input type="checkbox"/>	Box No. VIII (iii) Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	
<input type="checkbox"/>	Box No. VIII (iv) Declaration of inventorship (only for the purposes of the designation of the United States of America)	
<input type="checkbox"/>	Box No. VIII (v) Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	

PCT Request Sheet 6

Supplemental Box IV: PRIORITY CLAIM		
Filing Date of Earlier Application (day/month/year)	Number of Earlier Application	National Application Country
6 September 2002 (06.09.02)	10/237,138	US

Box No. IX CHECK LIST; LANGUAGE OF FILING

This international application contains:		This international application is accompanied by the following item(s) (mark the applicable check-boxes below and indicate in right column the number of each item):	Number of items
(a) the following number of sheets in paper form:			
request (including declaration sheets)	: 8		
description (excluding sequence listing part)	: 122		
claims	: 10		
abstract	: 1		
drawings	: 25		
Sub-total number of sheets	166		
sequence listing part of description (actual number of sheets if filed in paper form, whether or not also filed in computer readable form; see (b) below)			
Total number of sheets	166		
(b) sequence listing part of description filed in computer readable form			
(i) <input type="checkbox"/> only (under Section 801(a)(i))			
(ii) <input type="checkbox"/> in addition to being filed in paper form (under Section 801(a)(ii))			
Type and number of carriers (diskette, CD-ROM, CD-R or other) on which the sequence listing part is contained (additional copies to be indicated under item 9(ii), in right column):			
Figure of the drawings which should accompany the abstract: 3C			
		Language of filing of the international application: English	

Box No. X SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

Morey B. Wildes

Date: January 7, 2003

For receiving Office use only		2. Drawings: <input type="checkbox"/> received: <input type="checkbox"/> not received:
1. Date of actual receipt of the purported international application:		
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:		
4. Date of timely receipt of the required corrections under PCT Article 11(2):		
5. International Searching Authority (if two or more are competent): ISA /	6. <input type="checkbox"/> Transmittal of search copy delayed until search fee is paid	

For International Bureau use only

Date of receipt of the record copy by the International Bureau: